Meta-analysis of efficacy and safety of intravenous ferric carboxymaltose (Ferinject) from clinical trial reports and published trial data

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CRD summary
There was much evidence that intravenous ferric carboxymaltose was effective in treating iron-deficiency anaemia, from many chronic conditions, but little evidence comparing different preparations. The effects were large, so the broad conclusions may be appropriate, but flaws in the review process and substantial variation across studies, suggest that the results may not be reliable and generalisable across conditions.

Authors' objectives
To investigate the efficacy and safety of intravenous ferric carboxymaltose (Ferinject) for the treatment of iron-deficiency anaemia.

Searching
PubMed was searched up to February 2011. Some search terms were presented. Reports of clinical trials that were completed by March 2010 were provided by Vifor Pharma UK Limited, the manufacturer of Ferinject. The reference lists of the identified articles, reviews and clinical trial reports were checked.

Study selection
Randomised controlled trials (RCTs) and cohort studies, which used intravenous ferric carboxymaltose, in the treatment of iron-deficiency anaemia, were eligible if they included at least 10 patients. Studies were eligible regardless of the cause of anaemia, the study duration, and the age of the patients. The outcomes of interest were: treatment success (as defined in each study); the attainment of a normal haemoglobin level; increases in haemoglobin, serum ferritin, and ferritin; and transferrin saturation. Withdrawals and a range of adverse events were considered.

The included studies examined patients with: chronic kidney disease, on haemodialysis, postpartum anaemia, uterine bleeding, inflammatory bowel disease, congestive heart failure, gastrointestinal disease, or general iron-deficiency anaemia. Most studies used oral iron as the comparator, but some used intravenous iron sucrose or placebo. The average age of patients ranged from 26 to 70 years. Dosing varied; generally up to 1g of iron per week was given.

The number of reviewers who selected studies was not stated.

Assessment of study quality
Quality was assessed using the Oxford Quality Scale (also known as the Jadad), for randomisation, blinding and reporting of drop-outs. A score of 5 was highest quality, with scores of 3 or more judged to be a low risk of bias.

The number of reviewers who performed the assessment was not stated.

Data extraction
For dichotomous outcomes, such as treatment success and adverse events, the data were extracted to calculate relative risks, with corresponding 95% confidence intervals. For continuous outcomes, such as the change in haemoglobin level, mean differences, with 95% confidence intervals, were extracted.

The number of reviewers who extracted the data was not stated.

Methods of synthesis
For all outcomes, the study data were combined in fixed-effect meta-analyses to produce summary relative risks or mean differences. For dichotomous outcomes, the number needed to treat was calculated and heterogeneity was assessed using L'Abbe plots and subgroup analyses. For continuous outcomes, heterogeneity was assessed using $I^2$. Where studies were deemed unsuitable for pooling, a narrative description was given.
Results of the review

Eleven RCTs and three cohort studies were included. Intravenous ferric carboxymaltose was administered to 348 patients in the cohort studies, and 2,348 patients in the trials, with 832 patients receiving oral iron, 384 receiving iron sucrose, and 762 receiving placebo. Treatment lasted from one to 24 weeks. Three trials scored 5 for quality, seven (all non-blinded) scored 3, and one scored 2.

Compared with oral iron, intravenous ferric carboxymaltose increased haemoglobin levels (MD 4.80g/L, 95% CI 3.28 to 6.33; five trials; I²=55%). It increased the likelihood of achieving the target haemoglobin level (RR 1.3, 95% CI 1.2 to 1.4; five trials), and the chance of clinical success (RR 250, 95% CI 51 to 1,190; three trials). Compared with all other treatments, where the results were presented, they were similar.

Compared with oral iron, intravenous ferric carboxymaltose increased ferritin levels (MD 163 micrograms per litre, 95% CI 153 to 173; five trials; I²=98%), and transferrin saturation levels (MD 5.29%, 95% CI 3.74 to 6.83; five trials; I²=88%). Compared with all other treatments, intravenous ferric carboxymaltose had fewer withdrawals (RR 0.8, 95% CI 0.6 to 0.9; 10 trials), but possibly (not statistically significant) increased adverse events (RR 1.1, 95% CI 1.0 to 1.2; eight trials).

Compared with oral iron, intravenous ferric carboxymaltose lowered the risk of gastrointestinal events (RR 0.44, 95% CI 0.36 to 0.54; five trials), but produced more general and administrative events (RR 2.8, 95% CI 1.9 to 4.2; five trials) and more nutrition and metabolism abnormalities (RR 2.2, 95% CI 1.4 to 3.4; four trials). It also produced more gastrointestinal and general and administrative events than placebo (two trials each). Further results were presented.

Cost information

One trial found that intravenous ferric carboxymaltose had a lower cost and higher success rate than intravenous iron sucrose.

Authors’ conclusions

There was much evidence that intravenous ferric carboxymaltose was effective in treating iron-deficiency anaemia, from many chronic conditions, but there was limited evidence comparing different intravenous iron preparations.

CRD commentary

This review addressed an appropriate research question, with broad inclusion criteria. Only one database was searched, so relevant studies may have been missed, and publication bias cannot be ruled out. Some unpublished data, from clinical trial reports, were provided by the manufacturer, who funded this review. It was not clear if any effort was made to reduce the risks of reviewer error and bias in the review process.

Study quality was assessed and most were judged to be at a low risk of bias, but most trials were not blinded. Study data were combined using fixed-effect meta-analysis, which was not appropriate, given the substantial heterogeneity across trials, and the diversity in medical conditions and treatment comparators. The possible causes of heterogeneity were not investigated.

The identified treatment benefits were large, so the authors’ broad conclusions may be appropriate, but flaws in the review process, and the considerable variation across trials, suggest that the results may not be reliable and may not be generalisable across all patient populations and medical conditions.

Implications of the review for practice and research

The authors gave no recommendations for practice and research, beyond those in their conclusions.

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Bibliographic details

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